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(54) Title: NANOCOMPOSITE DRUG DELIVERY COMPOSITION

(57) Abstract: The invention relates to a drug delivery composition comprising an active ingredient and a biologically inert material wherein the biologically inert material is a nanocomposite material. Preferably the biologically inert material is a polymer-clay nanocomposite comprising up to about 40% by weight of nano-sized (1-1000nm) clay particles dispersed in a polymeric material. The active ingredient may be dispersed in the nanocomposite material or absorbed thereto.

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Nanocomposite Drug Delivery Composition

The present invention relates to the use of a nanocomposite material in drug delivery compositions.

It is well recognised that there are a number of circumstances whereby it is desirable to disperse a drug in a biologically inert matrix in the preparation of a final dosage form. For example, the incorporation of drugs and bioactive molecules into polymeric matrices (eg implants, solid dispersions) has attracted considerable interest as a means of improved drug delivery. Similarly, drug or bioactive-loaded microspheres and nanospheres have received considerable attention. Various drug delivery compositions comprise modified release systems whereby the drug is released at a controlled rate so as to optimise biological activity and therapeutic effect of the drug (eg controlled release oral drug delivery systems). Another example is the use of drug-loaded medical devices, whereby polymeric devices such as stents may contain antibiotics or anticoagulants for purposes such as the prevention of microbial growth. A further example is the use of tissue engineering scaffolds, whereby growth factors may be incorporated into a polymeric matrix to optimise cell growth on that matrix. In all cases it is necessary to produce systems that not only release the drug at an appropriate rate but also have suitable mechanical properties for the particular application.

Nanocomposites are materials that consist of particles of one compound with a mean diameter in the nano-size range (1-1000nm) dispersed throughout another material, commonly a modified inorganic clay dispersed within an organic polymer. These polymer-clay nanocomposites (PCNs) possess advantageous properties compared to the polymer alone such as increased mechanical strength, reduced gaseous permeability and higher heat resistance, even though the quantity of clay may be 5% or less. Nanocomposite materials have attracted great interest due to the wide range of alterations in the properties of the base polymer engendered by the incorporation of the clays (see for example Schmidt et al, Current Opin.Solid State Mat.Sci. (2002) 6, 205-212; Choi et al, Chem.Mater. (2002) 14, 2936-2939; T.J. Pinnavaia and G.W. Beall, "Polymer-clay nanocomposites", Wiley, Chichester, 2001). Moreover, they may be manufactured by a range of techniques using equipment that is well established and hence are economical to produce (depending on the choice of materials, although commonly the materials used are well recognised and inexpensive).

The use, in drug delivery compositions, of potentially useful matrix materials can be limited by their mechanical properties. The matrix must maintain suitable mechanical integrity during the course of the manufacture process and through its subsequent handling and use.

There are many instances whereby the mechanical properties and / or the release rate of the drugs or bioactives of known drug delivery compositions are sub-optimal. The present invention providing as it does for drug or bioactive-loaded nanocomposites seeks to address these difficulties.

Therefore, it is an object of the present invention to provide a drug delivery composition wherein the release rate of the drug may be manipulated or altered so as to be optimised for a given drug or application.

It is another object of the invention to provide a drug delivery composition which is mechanically suitable for the application to which the drug delivery composition is to be put and which is capable of maintaining mechanical integrity throughout the course of its manufacture, storage, handling and use as appropriate.

It is a further object of the invention to provide a drug delivery composition the manufacture of which may be carried out economically viable using equipment that is readily available.

Accordingly, the present invention provides for the use of a nanocomposite material in the manufacture of a drug delivery composition.

The invention also provides a drug delivery composition comprising an active ingredient and a

biologically inert material wherein the biologically inert material is a nanocomposite material, preferably a polymer-clay nanocomposite.

Preferably the active ingredient is dispersed throughout a matrix comprising the biologically inert material, although the invention also provides a drug delivery system wherein the active ingredient is loaded in, or adsorbed to, a vehicle comprising the biologically inert material.

The invention further provides a method of manufacturing a drug delivery composition comprising the steps of forming an admixture comprising a polymer, a clay and an active ingredient and extruding the admixture to produce an extrudate.

The nanocomposite material may comprise up to about 99.9% w/w polymer. Preferably the polymer is present in an amount of from about 90% w/w to about 99% w/w of the nanocomposite.

A wide range of polymers may be employed in the biologically inert material. Examples of suitable polymers include polyethylene glycol, poly(ε-caprolactone), polyvinylpyrrolidone, polylactide, polyethylene, polystyrene, poly(dimethylsiloxane), polyaniline, polyester, polyimide, cellulose derivatives such as hydroxyproyl methyl cellulose and ethylcellulose, polysaccharides such as alginates and chitosans, gelatin, polymethylmethacrylates, silicones,

polyacrylonitrile, polyetheretherketone (PEEK), polyamide, polyurethane, bone and dental cements and other polymeric prosthetic materials. In addition materials such as starch and starch derivatives would also be suitable for use in the inert material. Materials that are composed of more than one polymer or a polymer and a plasticizer such as polyethylene glycol, water or glycerol may also be included.

Typically the level of clay within the nanocomposite may range from less than 1% w/w to about 40% w/w, although higher levels may be included. Preferably the amount of clay in the nanocomposite is within the range of from 1% w/w to 10% w/w of the nanocomposite material.

Various clays may be used, either alone or in combination. Typically silicates may be used that may be naturally occurring (for example bentonite, montmorillonite and other smectites) or synthetic (for example fluorohectorite, fluoromica, layered double hydroxides).

The presence of the clay nanoparticles can dramatically alter the mechanical properties of the composition of the invention, compared to a conventional drug delivery vehicle using a polymer-only matrix, so as to render the system much more suitable for a particular application. The mechanical properties of the drug delivery composition of the invention may be manipulated by

suitable choice of nanocomposite component materials (ie the polymers and clays used) and / or manufacturing conditions. Furthermore, the rate at which the composition biodegrades may differ from that of the polymer alone and may be tailored to suit a particular active ingredient or therapeutic application.

The teaching of the invention is applicable to all such methods of nanocomposite manufacture and to all active ingredients (drugs and bioactive materials including growth factors, nutraceuticals, antimicrobials and the like) which can withstand the manufacturing conditions. Suitable drugs and bioactives include for example low molecular weight compounds such as indomethacin and paracetamol, higher molecular weight compounds such as hydrocortisone, peptides such as cyclosporin A and calcitonin and proteins such as insulin and human recombinant DNAse. The manufacturing method used may be tailored to suit both the performance requirements of the composition and the lability of the incorporated bioactive such that degradation may be minimised by appropriate choice of manufacturing method.

The amount of active ingredient employed in the drug delivery composition of the present invention may vary depending on the characteristics of each particular agent. However, the active ingredient should be employed in an amount which is sufficient to elicit a therapeutic response upon release from

the drug delivery composition. Typically the active ingredient may be employed in an amount of from less than 1% to about 40% by weight of the composition.

A drug delivery composition of the invention may be prepared according to any known method of manufacturing nanocomposites which can be modified so as to facilitate the incorporation of the drugs or bioactive molecule, for example by melt extrusion. Other manufacturing methods include *in situ* polymerisation (Paul et al, (2003) Polymer, 44, 443-450), melt intercalation (Lepoittevin et al (2002) Polymer 43, 4017-4023), sonication (Burnside and Giannelis (1995) Chemistry of Materials, 7, 1597-1600) sol-gel technology and solution blending.

In the case of manufacture by melt extrusion, the various components may be mixed simultaneously (prior to extrusion) in order to disperse the active ingredient throughout the nanocomposite material, although the mixing sequence can influence the product structure and performance and represents another means by which the properties and release characteristics of the composition may be controlled. Other factors such as the choice of extrusion screw geometries may influence the structure and performance of the extrudate. The drug-loaded nanocomposite extrudate produced may be ground and then formulated into dosage forms such as tablets and capsules. In such cases, the person skilled in the art would appreciate that excipients such as diluents, lubricants, glidants,

disintegrants and the like may be utilised in preparation of the final dosage form. Further modifications known in the field of formulation chemistry, such as the application of enteric or taste masking coatings to tablets for example, may be employed.

Dosage forms categories for which the invention may be particularly useful include oral drug delivery systems for modified (fast or slow) release, implant systems (biodegradable or non-biodegradable), microspheres and nanoparticles for oral, nasal, parenteral or topical delivery, medical devices, suppositories, pessaries, dermatological preparations, tissue engineering scaffolds.

The present invention also provides a drug delivery system wherein an active ingredient loaded in, or adsorbed to, a vehicle comprising the biologically inert material, the biologically inert material being a nanocomposite material. The use of nanocomposites in the manufacture of drug-loaded medical devices (for example devices such as stents containing antibiotics or anticoagulants) affords similar advantages as those discussed above in terms of controlled active ingredient delivery and robustness.

Example 1

Drug dispersions in polyethylene glycol based nanocomposites for the oral administration of drugs were prepared as follows:

Polyethylene glycol (PEG) 20000 (Janssen Pharmaceuticals) was the polymer employed and Cloisite 30B (Southern Clay Products, USA) was the clay component. Paracetamol (Sigma, UK) was used as a model active ingredient. Production of the nanocomposites was performed by melt extrusion using a Killon KN-100 (Davis Standard Corporation, USA) single screw extruder with rod shaped die (38 mm screw diameter, speed 20-22 rpm, die temp 54-57 °C, temperature zone 1 50 °C - temperature zone 2 55-60 °C - temperature zone 3 55-60 °C - temperature zone 4 55-60 °C, haul off speed 3-4 m/min, cool to room temperature). The powders were not subjected to any treatments prior to extrusion, other than simple mixing of the three components simultaneously.

The following combinations were used (all % values are percentages by weight:

- Paracetamol capsule (number 3, white, gelatin capsule)
- 5% paracetamol in PEG (pPEG)
- paracetamol 5%/Cloisite 30B 4% /PEG 95% (the drug loaded nanocomposite of the invention)

The extrudates emerged as cylindrical solid tube-like structures of approximately 5 mm in diameter.

During the processing of pPEG the following readings were obtained: screw amps: 4; die pressure: 0.1 kg/cm^2; however when the nanocomposite mixture was extruded the screw amps and die pressure values increased to 8 and 0.4 respectively evidencing the enhanced mechanical strength and resistance of the nanocomposites. Extrusion conditions were optimised by initially heating the system to beyond the melting point of the PEG (circa 60°C) and cooling to circa 56°C so as to extrude the material when in a supercooled state thus facilitating rapid solidification upon extrusion from the equipment. The nanocomposite extrudates produced were mechanically robust and could be snapped by manual application of pressure.

In testing the release characteristics of each sample the following dissolution methodology was used (Copley DIS 8000): USP apparatus 2 - rotating paddle, 50 rpm; medium - 900 ml deionised water (37 °C ± 0.5 °C); analysis - UV spectrophotometer (243 nm).

Dissolution properties were measured as follows: A UV calibration plot from a stock solution of paracetamol was prepared (100mg in 100ml), with measurements taken at 249nm. Five samples were used for each experiment with 10ml removed at appropriate time intervals and replaced with 10mls 37°C deionised water. The samples were analysed using UV measurement at 249nm. Samples were prepared by breaking the extrudate into approximately 1cm

lengths, with a corresponding sample weight of circa 0.3g. For the pPEG samples, samples were taken every 5 minutes for 30 minutes. For the nanocomposite composition samples were taken every 20 minutes for 4 hours.

The release profiles of the three combinations tested are shown in Figure 1. The release profile of the paracetamol nanocomposite of the invention indicates a slower release rate plateauing at about 60 min compared to rate of release from the paracetamol capsule which reached a plateau at about 30 min. The release profile of the pPEG sample was faster that both the drug loaded nanocomposite of the invention and the paracetamol capsule, plateauing after about 20 min.

The test data indicates that the nanocomposite system may be used as a controlled release drug delivery system whereby drug release from the composition is slowed or otherwise manipulated in comparison to the non-clay containing system.

Example 2

A further drug delivery composition, in the form of a drug loaded polyurethane nanocomposite for use in an insert device, was prepared as follows:

The polymer / clay / drug composition was thermoplastic polyurethane (95 %) / Cloisite 30B (4 %) / hydrocortisone (1 %). The mixture of

constituents was extruded using a Collin GmbH twin screw extruder (Model ZK 25), adapter temperature 190 °C, die temperature 19 °C, melt temperature 188 °C, melt zones on the extruder were set between 195 °C and 190 °C from the feed end and screw speed was 90 rpm. The mixture was extruded through a cast film die to produce 200 micron thick, 40 to 50 mm wide film of the drug loaded nanocomposite.

CLAIMS

1. A drug delivery composition comprising an active ingredient and a biologically inert material wherein the biologically inert material is a nanocomposite material.

2. A drug delivery composition according to Claim 1 wherein the active ingredient is dispersed throughout a matrix comprising the biologically inert material.

3. A drug delivery composition according to either of Claims 1 and 2 wherein the nanocomposite is a polymer-clay nanocomposite.

4. A drug delivery composition according to any one of Claims 1 to 3 wherein the nanocomposite comprises at least one polymer selected from the group consisting of polyethylene glycol, poly(ε-caprolactone), polyvinylpyrrolidone, polylactide, polyethylene, polystyrene, poly(dimethylsiloxane), polyaniline, polyester, polyimide, cellulose derivatives such as hydroxyproyl methyl cellulose and ethylcellulose, polysaccharides such as alginates and chitosans, gelatin, polymethylmethacrylates, silicones, polyacrylonitrile, PEEK, polyamide, polyurethane, bone and dental cements, starch and starch derivatives.

5. A drug delivery composition according to any one of Claims 1 to 4 wherein the nanocomposite comprises at least one clay selected from the group consisting of bentonite, montmorillonite, fluorohectorite, fluoromica and layered double hydroxides.

6. A drug delivery composition according to any one of Claims 1 to 5 wherein the amount of clay within the nanocomposite is up to 40% w/w of the nanocomposite material.

7. A drug delivery composition according to any one of Claims 1 to 5 comprising at least one active ingredient selected form the group consisting of indomethacin, paracetamol, hydrocortisone, cyclosporin A, calcitonin, insulin and human recombinant DNAse.

8. A drug delivery composition according to any one of Claims 1 to 7 wherein the active ingredient is present in an amount of up to 40% by weight of the drug delivery composition.

9. A drug delivery system wherein an active ingredient loaded in, or adsorbed to, a vehicle comprising the biologically inert material wherein the biologically inert material is a nanocomposite material.

10. A drug delivery system where the nanocomposite material is a polymer-clay nanocomposite.

11. A drug delivery system according to either of Claims 9 and 10 wherein the nanocomposite comprises at least one polymer selected from the group consisting of polyethylene glycol, poly(ε-caprolactone), polyvinylpyrrolidone, polylactide, polyethylene, polystyrene, poly(dimethylsiloxane), polyaniline, polyester, polyimide, cellulose derivatives such as hydroxyproyl methyl cellulose and ethylcellulose, polysaccharides such as alginates and chitosans, gelatin, polymethylmethacrylates, silicones, polyacrylonitrile PEEK, polyamide, polyurethane, bone and dental cements, starch and starch derivatives.

12. A drug delivery system according to any one of Claims 9 and 11 wherein the nanocomposite comprises at least one clay selected from the group consisting of bentonite, montmorillonite, fluorohectorite, fluoromica and layered double hydroxides.

13. A drug delivery system according to any one of Claims 9 to 12 wherein the amount of clay within the nanocomposite is up to 40% w/w of the nanocomposite.

14. A drug delivery system according to any one of Claims 9 to 13 comprising at least one active ingredient selected form the group consisting of indomethacin, paracetamol, hydrocortisone,

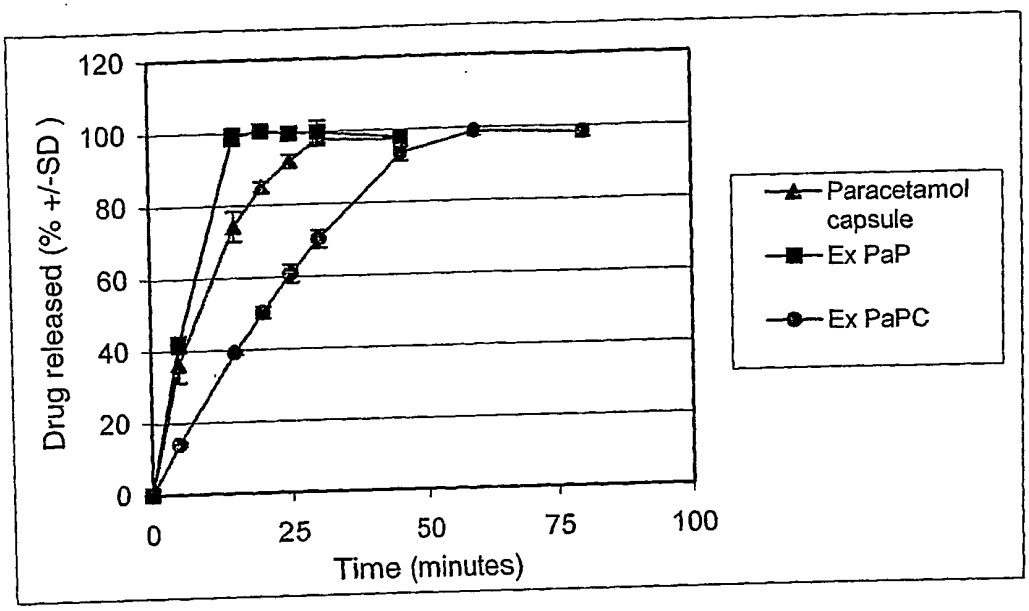
cyclosporin A, calcitonin, insulin and human recombinant DNAse.

15. A drug delivery system according to any one of Claims 9 to 14 wherein the active ingredient is present in an amount of up to 40% by weight of the drug delivery system.

16. A method of manufacturing a drug delivery composition comprising the steps of forming an admixture comprising a polymer, a clay and an active ingredient and extruding the admixture to produce an extrudate.

17. A drug delivery composition as defined in any one of Claims 1 to 8 when produced by a method according to Claim 16.

18. A drug delivery composition substantially as hereinbefore described.



▲ paracetamol capsule

■ paracetamol in PEG (pPEG)

● paracetamol loaded nanocomposite of the invention

Figure 1.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/51

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, MEDLINE, EMBASE, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97/13503 A (SELVARAJ ULAGARAJ ; MESSING GARY L (US); PENN STATE RES FOUND (US)) 17 April 1997 (1997-04-17) examples 2-5 claims 1,2,4,7,9,15,22	1-18
X	US 2002/164482 A1 (AU MING ET AL) 7 November 2002 (2002-11-07) paragraphs '0006!, '0007!, '0087!, '0090!, '0146!, '0159! claims 1,2,4	1-18
X	US 5 683 719 A (NEWTON JOHN MICHAEL) 4 November 1997 (1997-11-04) example 1 claims 1-3,8,9	16-18

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2004/001931

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	CYPES S H ET AL: "Organosilicate-polymer drug delivery systems: controlled release and enhanced mechanical properties" JOURNAL OF CONTROLLED RELEASE, ELSEVIER SCIENCE PUBLISHERS B.V. AMSTERDAM, NL, vol. 90, no. 2, 24 June 2003 (2003-06-24), pages 163-169, XP004431309 ISSN: 0168-3659 abstract	1-18
A	US 2003/065355 A1 (WEBER JAN) 3 April 2003 (2003-04-03) the whole document	1-18
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INTERNATIONAL SEARCH REPORT

Information on patent family members

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